Review Article

TIPS Trends in Pharmaceutical Sciences 2025: 11(1): 73-86.

Mechanism of Interaction between Nanoparticles and the Body: Molecular, Cellular, and Tissular Levels – a review

Mohammed Khalid[1*];Ph.D ,Ashok Kumar BS[2];Ph.D , Disha NS[3];Ph.D, Chaithanya A[3];Ph.D

[1]Department of Pharmaceutics, R.L Jalappa College of Pharmacy, Sri Devaraj Urs Academy Higher Education and Research (a Deemed to be University), Tamaka, Kolar, India.
[2]Department of Pharmacognosy, R.L Jalappa College of Pharmacy, Sri Devaraj Urs Academy Higher Education and Research (a Deemed to be University), Tamaka, Kolar, India.
[3]Department of Pharmaceutical Chemistry, R.L Jalappa College of Pharmacy, Sri Devaraj Urs Academy Higher Education and Research (a Deemed to be University), Tamaka, Kolar, India.

Abstract

Nanoparticles (NPs), ranging from 1 to 100 nanometers, exhibit unique properties that enable their use in medical applications such as drug delivery, diagnostics, and therapies. Their interactions with biological systems occur at molecular, cellular, and tissue levels, significantly influencing their behavior and efficacy. At the molecular level, NPs form a dynamic protein corona in biological fluids, affecting cellular uptake and biodistribution. NPs also interact with lipids and nucleic acids, impacting membrane integrity and gene delivery. Cellular uptake of NPs involves various endocytic pathways, influencing intracellular trafficking and potential cytotoxicity. Tissue-level interactions determine NP biodistribution, with accumulation in organs like the liver, spleen, and brain posing both therapeutic opportunities and safety concerns. Comprehensive studies on NP safety, biocompatibility, and regulatory guidelines are essential for advancing nanomedicine. This review delves into the mechanisms of these interactions, referencing key studies and highlighting their implications for the development of nanomedicine.

Keywords: Nanoparticles, Molecular interaction, Biocompatibility, Nanomedicines.

Please cite this article as: Mohammed Khalid, Ashok Kumar BS, Disha NS, Chaithanya A. Mechanism of Interaction between Nanoparticles and the Body: Molecular, Cellular, and Tissular Levels – a review. Trends in Pharmaceutical Sciences. 2025;11(1):73-86. doi: 10.30476/tips.2024.103004.1245

1. Introduction

Nanoparticles (NPs) have received considerable attention recently due to their distinctive properties and potential applications in diverse fields, particularly in medicine. Defined as particles ranging from 1 to 100 nanometers in size, NPs exhibit unique physical and chemical characteristics that differ significantly from their larger-scale counterparts. These properties, such as their high surface area-to-volume ratio, quantum effects, and ability to bind with various biological molecules, enable NPs to interact with biological systems in innovative and often advantageous ways (1).

Their potential in medicine spans drug delivery systems, diagnostic tools, and therapeutic agents. For example, NPs can be engineered to deliver drugs directly to specific cells or tissues, thereby enhancing treatment effectiveness and reducing side effects. In diagnostics, NPs improve the accuracy and sensitivity of imaging techniques, aiding in early disease

Corresponding Author: Mohammed Khalid, Department of Pharmaceutics, R.L Jalappa College of Pharmacy, Sri Devaraj Urs Academy Higher Education and Research (a Deemed to be University), Tamaka, Kolar, India.
Email address: khaliddear1212@gmail.com

Received: 16/01/2025; Accepted: 01/03/2025

detection and monitoring. Furthermore, NPs themselves are being investigated as therapeutic agents, such as in the application of photothermal therapy for cancer treatment. Despite these promising applications, the interaction of NPs with biological systems is intricate and multifaceted, occurring at molecular, cellular, and tissue levels. Understanding these interactions is essential for the safe and effective development of nanomedicine applications. At the molecular level, NPs interact with proteins, lipids, and nucleic acids, which can significantly alter their biological behavior and identity. These interactions influence how NPs are taken up by cells, their distribution throughout the body, and their potential toxicity. The physicochemical properties of NPs, including their size, shape, surface charge, and coatings, dictate the nature of these interactions (2). Once inside cells, NPs can induce oxidative stress, provoke inflammatory responses, or even cause cell death, underscoring the need for thorough assessment of their biocompatibility and potential cytotoxicity. Factors such as NP size, surface characteristics, and the body's physiological conditions determine their distribution across different organs and tissues. Understanding the mechanisms governing NP accumulation in specific tissues, such as the liver, spleen, and brain, is crucial for designing NPs that exhibit desired biodistribution profiles with minimal adverse effects. Given the complexity of NP interactions with biological systems, a comprehensive understanding of these mechanisms is imperative for advancing nanomedicine (3). This review aims to provide a detailed exploration of NP interactions at molecular, cellular, and tissue levels, drawing on recent studies to elucidate these interactions. By enhancing our understanding of NP behaviour in biological contexts, we can better leverage their potential for medical applications while mitigating associated risks.

2. Molecular Level Interactions

When nanoparticles (NPs) enter biological fluids, they quickly become coated with a layer of biomolecules, primarily proteins, forming a "protein corona." This corona defines the biological identity of the NP and influences its interactions with cells and tissues. The protein corona's composition is highly dynamic, evolving over time and in different biological environments. Initially, proteins with a high affinity for the NP surface bind rapidly, forming a primary corona. As the NP circulates through various biological compartments, proteins with lower affinity may replace or layer on top of the primary corona, creating a secondary corona (4). This dynamic process results in a complex and heterogeneous mixture of proteins on the NP surface. Recent studies have shown that the protein corona can alter the hydrodynamic diameter and surface charge of NPs, which in turn affects their cellular uptake and biodistribution. Key factors influencing protein corona formation include NP properties, the composition of the biological fluid, and surface modifications of the NP. The protein corona mediates the biological identity of NPs, affecting their recognition and clearance by the immune system, their cellular uptake mechanisms, and their overall biodistribution in vivo. It can also influence the therapeutic efficacy and safety of NP-based treatments and diagnostics (2). For instance, NPs with different protein coronas exhibit varying degrees of cellular uptake and inflammatory response.

2.1. Interactions with Lipids and Nucleic Acids

Beyond proteins, NPs also interact with lipids and nucleic acids, which can affect cellular membranes and genetic materials.

2.1.1. Lipid Membrane Interactions

NPs interact with cellular lipid membranes through mechanisms such as direct penetration or endocytic uptake pathways. The physicochemical properties of NPs, including size, shape, and surface charge, determine their interaction with lipid bilayers. Some NPs can disrupt lipid bilayers, leading to membrane damage and potential cytotoxic effects (5). Understanding these interactions

is crucial for assessing NP biocompatibility and designing safer nanomedicine formulations. Surface modifications with lipids or lipid-like molecules can enhance NP stability and biocompatibility. Lipid-coated NPs mimic biological membranes, potentially reducing immune recognition and improving circulation time in vivo. Lipid-based NPs are used in drug delivery systems due to their ability to encapsulate hydrophobic drugs and target specific cells or tissues. For example, liposomes, which have a lipid bilayer structure, provide stability to encapsulated drugs and enable targeted delivery, highlighting the significance of lipid-NP interactions in therapeutic applications. NPs can interact with high-density lipoprotein (HDL) and other lipoproteins in biological fluids, altering their biodistribution and clearance profiles. These interactions can impact NP pharmacokinetics and therapeutic efficacy. A study investigating the renal clearance of quantum dots (QDs) after systemic administration found that lipid-PEG (polyethylene glycol) coated QDs exhibited prolonged circulation times due to reduced recognition by opsonins and enhanced interaction with lipoproteins, underscoring the role of lipid coatings in NP biodistribution (6).

2.1.2. Interactions with Nucleic Acids

NPs are used as vectors for delivering nucleic acids (e.g., DNA, RNA) into cells for gene therapy applications. Surface modifications and complexation strategies enable NPs to protect nucleic acids from degradation and facilitate their intracellular delivery. NPs can deliver small interfering RNA (siRNA) or microRNA (miRNA) to silence specific genes in therapeutic interventions. For effective gene silencing, nucleic acid-NP complexes must efficiently enter cells and release their cargo (7). NPs protect siRNA from enzymatic degradation and facilitate cellular uptake, illustrating the importance of NP-nucleic acid interactions in enhancing therapeutic gene silencing. NPs can complex with nucleic acids through electrostatic interactions or encapsulation within particles like liposomes and polymeric NPs, protecting the nucleic acids from enzymatic degradation and enhancing stability in biological environments (8). For instance, lipid-coated polymeric NPs have been used to deliver mRNA vaccines to dendritic cells, with the lipid coating protecting the mRNA and promoting uptake by immune cells, leading to potent antitumor immune responses. NPs carrying nucleic acids may trigger innate immune responses via pattern recognition receptors (PRRs). Surface modifications and formulation strategies are employed to mitigate immunogenicity and improve therapeutic outcomes. Functionalizing NPs with targeting ligands such as aptamers or antibodies enhances their specificity for cells expressing particular receptors, facilitating targeted delivery of nucleic acids to diseased tissues (9).

2.2. Cellular Level Interactions

NPs primarily enter cells through endocytosis, but the specific pathway depends on NP size, shape, and surface chemistry. Endocytosis involves the invagination of the cell membrane to form vesicles that internalize NPs, including subtypes such as clathrin-mediated endocytosis, caveolae-mediated endocytosis, and macropinocytosis (10). Phagocytosis, performed by specialized immune cells like macrophages, engulfs larger particles, including NPs, as a defense mechanism. Once inside the cell, NPs are trafficked to various organelles, impacting their biological activity and potential toxicity. NPs often travel through endosomes and lysosomes, encountering acidic environments and degradative enzymes, with some NPs able to escape into the cytoplasm (11). Interactions with the endoplasmic reticulum (ER) and Golgi apparatus can disrupt protein folding, modification, and trafficking, leading to cellular stress. For example, a study on the cellular uptake and behavior of quantum dots (QDs) used for imaging and sensing found that QD uptake mechanisms var-

ied with size and surface chemistry. Smaller QDs (<10 nm) were internalized via clathrin-mediated endocytosis, while larger QDs (>20 nm) were taken up through macropinocytosis. PEGylation reduced nonspecific binding and enhanced QD stability and biocompatibility. Intracellular trafficking showed QDs localized in endosomes and lysosomes, affecting their cytotoxicity and biocompatibility. NPs can induce cytotoxicity through oxidative stress, inflammation, and cell death pathways (12). They can generate reactive oxygen species (ROS), causing oxidative damage to cellular components, including lipids, proteins, and DNA. NPs can activate immune cells to produce pro-inflammatory cytokines, leading to inflammatory responses that may cause tissue damage, and can trigger programmed cell death (apoptosis) or necrotic cell death through various molecular pathways, disrupting cellular homeostasis (13).

2.3. Tissue Level Interactions

NPs exhibit unique biodistribution profiles influenced by their physicochemical properties and the biological characteristics of different tissues. Understanding NP accumulation in specific tissues is crucial for targeted delivery and minimizing off-target effects (14). For instance, a study on the tissue distribution and pharmacokinetics of pegylated liposomal doxorubicin (Doxil), a common NP-based chemotherapy, found that pegylation prolonged circulation time and modified tissue distribution compared to conventional liposomes. Doxil showed enhanced tumor accumulation due to the enhanced permeability and retention (EPR) effect but also prolonged circulation in the liver and spleen, affecting therapeutic efficacy and toxicity (15). NPs tend to accumulate in organs like the liver, spleen, and lungs, with the liver and spleen being primary sites due to their roles in blood filtration and high phagocytic activity. The ability of NPs to cross the blood-brain barrier (BBB) is critical for treating neurological diseases but raises concerns about potential neurotoxicity. For example, it was demonstrated that polysorbate-coated NPs could cross the BBB and deliver drugs to the brain, enhancing the treatment of central nervous system disorders. This review discusses various nanoparticulate systems designed to overcome the BBB and improve drug delivery to the brain, highlighting their potential in neurotherapeutics (16). NPs can interact with immune cells, either activating or evading the immune system, impacting their use in vaccines and immunotherapies. The review covers the immunological properties of engineered nanomaterials and their implications for tissue interactions. NPs can trigger immune responses, including complement activation and cytokine release, affecting their biodistribution and biocompatibility. Surface modifications like PEGylation can mitigate immune recognition, prolong NP circulation, and enhance tissue-specific targeting. NPs can be recognized by pattern recognition receptors (PRRs) on immune cells, leading to immune activation, beneficial for vaccine adjuvants but potentially causing unwanted inflammation. Certain NPs are designed to evade immune detection, enhancing circulation time and targeting efficiency, with surface modifications like PEGylation helping achieve this (17). NPs are also used in tissue engineering and regenerative medicine due to their ability to interact with and modulate cell behavior, promoting tissue repair. Incorporating NPs into scaffolds can enhance mechanical properties and bioactivity, aiding tissue regeneration. NPs can deliver growth factors, drugs, or genes in a controlled manner, enhancing the healing process in damaged tissues (18).

2.4. Variety of NPs interact with membrane and biological macromolecules

2.4.1 Polymeric nanoparticles (PNP)

Polymeric nanoparticles are among the most adaptable and studied types of nanomaterials for drug delivery and biomedical purposes. The normal size ranges from 10

to 1,000 nanometres. They usually consist of biodegradable polymer where therapeutic agents are encapsulated against deterioration and hence their release, providing control while offering targeting. In fact, the interaction of biological membranes and macromolecules like proteins and nucleic acids will establish their functionality, hence their efficacy. PNPs can be prepared from a wide array of both natural and synthetic polymers. Currently, three general polymers used for drug-carrying nanoparticles are PLGA, PCL, and chitosan. The nature of physicochemical properties-size, surface charge, and hydrophobicity-of the nanoparticles depends on the type of selected polymer. This again will have implications for their interaction with biological systems. PLGA is one of those kinds of polymers preferred for their biocompatibility and biodegradability and good consideration in drug delivery. This can facilitate the delivery of drugs in a sustained way through gradual degradation (19). Such structural diversity in PNP offers various methods of drug loading, including encapsulation, adsorption, and covalent attachment of drugs to the polymer matrix. This flexibility in the design allows for the formulation of PNP able to bear a wide range of therapeutic agents, including small molecules, proteins, and nucleic acids.

2.4.2. Interaction with Biological Membranes

Such interaction of the PNP with cell membranes plays an important role in delivering active therapeutic agents. The general route of internalization of the PNPs into the cells is majorly through endocytosis, in which invagination of the cell membrane is seen to happen in vesicular form, thereby internalizing the nanoparticles (20). This efficiency depends on factors such as surface charge, size, and shape of the nanoparticles. Due to their surface charge, cationic PNPs have a positive surface charge and therefore interact well with the negatively charged phospholipid bilayer of cellular membranes. In principle, this enhances endocytosis but likely disrupts membrane integrity and causes cytotoxicity (21). Such issues may be partly resolved by surface modifications, including PEGylation. PEGylation decreases the surface charge and hydrophobicity of the PNPs, consequently decreasing their nonspecific interaction with the cell membrane and improving their biocompatibility. The size of the PNP affects cellular uptake and biodistribution. Smaller PNPs (<200 nm) are easily internalized within the cells through clathrin-mediated endocytosis, which is a commonly used pathway for nanoparticle uptake. Whereas this, due to cell type and nanoparticle surface properties, larger PNPs can be taken up through alternative mechanisms like macro pinocytosis or phagocytosis.

2.4.3. Interaction of Proteins

In the event of contact between PNPs with biological fluids, they highly tend to adsorb proteins on their surface forming something about "protein corona." This layer of adsorbed protein helps in modifying nanoparticle surface properties and, due to its nature, determines its biological identity. The composition of protein corona is dynamic and depends mostly on the physicochemical properties of PNPs and available proteins in the biological environment. The protein corona can affect cellular uptake and biodistribution of PNPs. The presence of opsonins, or opsonic proteins leads to rapid recognition and transport of PNPs through macrophages and decreases circulation time and therapeutic efficacy. In contrast, protein binding without consecutive immune recognition may result in prolonged circulation and accumulation of PNPs in target tissues. In addition, protein corona mediates the interaction between PNP and cellular receptors. This may lead to increased or inhibited cellular uptake, depending on the nature of proteins forming the corona and their affinity to specific cell surface receptors (22). Understanding and controlling protein corona formation is therefore a key factor for the de-

sign of PNPs with optimal therapeutic performance.

2.4.4. Interaction with Nucleic Acids: Gene Delivery Applications

PNPs are also intensively under study as vectors of nucleic acids in applications of gene therapy. The capability of PNPs to complex and protect nucleic acids, including DNA, RNA, and siRNA, against enzymatic degradation is a significant premise for accomplishing successful delivery of these biomacromolecules to the cellular target. One can engineer the release of nucleic acid cargo from PNPs under specific intracellular conditions, such as pH or redox potential. This makes the process of gene transfer so effective. In other words, this interaction of PNs and NA is a consequence of electrostatic interactions between the positively charged surfaces of the nanoparticles with negatively charged nucleic acids. It allows condensation of the nucleic acids to compact structures efficiently internalized by cells. Once inside the cell, PNPs must escape the endosomes and deliver their cargo into the cytoplasm, where the nucleic acids will act (23). Other than encapsulation of nucleic acids, PNPs can also be functionalized with targeting ligands such as peptides, antibodies, or aptamers, which enhance their specificity toward any type of cell or even tissues. Targeting increases the therapeutic index of these gene therapies through a greater nucleic acid concentration within diseased cells while minimizing off-target effects. While a considerable number of benefits are associated with drug delivery and gene therapy, the biocompatibility and potential cytotoxicity of the PNPs must be closely monitored. The interaction of cell membranes, biological macromolecules, and PNPs may provoke a host of adverse effects such as inflammation, oxidative stress, and apoptosis. Usually, these unwanted side effects are reduced by PEGylation or by using biocompatible polymers, hence increasing the safety profile of PNPs.

3. Polymeric Micelles

Polymeric micelles are an exciting class of nanoscale delivery systems exhibiting increasing interest in nanomedicine due to their unique structural features and their ability to solubilize hydrophobic drugs. Typically, the diameter of these globular structures is between 10 and 100 nanometres and results from the self-association of amphiphilic block copolymers in aqueous medium. These amphiphilic copolymers possess hydrophobic and hydrophilic segments capable of undergoing spontaneous self-association into micelles with hydrophobic segments at the core and hydrophilic segments at the corona or shell. The core-shell architecture typical for polymeric micelles is eminently useful in enclosing poorly water-soluble drugs and protecting such drugs from degradation with an enhanced bioavailability.

Basically, the polymeric micelles can be formed from the block copolymers that are made up of two or more chemically distinct polymer segments by covalent bonding. The hydrophobic segment constitutes the core of the micelle where hydrophobic drugs can be encapsulated, while the hydrophilic segment forms the outer shell interacting with the surroundings in an aqueous environment (24). PEG-PLA, PEG-PCL, and PEG-P(Asp) are some of the common block copolymers used for micelle formation. The polymeric micelles result as a result of a thermodynamically favored process above the concentration of block copolymers called critical micelle concentration, CMC. Above the CMC, hydrophobic segments of copolymers associate in order to minimize their exposure with aqueous environment and form a micellar core (25). Hydrophilic segments extend outwards, stabilizing micelle in solution.

It has been noticed that polymeric micelles have an advantage in the encapsulation of hydrophobic drugs inside their core, enhancing its solubility and stability in biologi-

cal fluids. Drugs can be physically entrapped within polymeric micelles or otherwise can be entrapped by chemical conjugation or through electrostatic interaction, depending on the nature of the drug and copolymer used. Generally, drug release from polymeric micelles may be controlled by degradation of the micellar core, drug diffusion out of the core, or environmental stimuli such as pH or temperature change (26). For instance, pH-sensitive polymeric micelles undergo structural changes in a tumor environment where the pH is normally significantly lower than in healthy tissues. This might lead to the drug's release directly within the tumor tissue with improved therapeutic effectiveness and reduced systemic toxicity.

3.1. Interaction with Biological Membranes

Thus, the principal interaction of polymeric micelles with biological membranes is by the process of endocytosis, in which the cells ingest the extracellular substances by forming vesicles around them (27). The cellular uptake and biodistribution of polymeric micelles are considerably influenced by their dimensions, surface charge, and surface modifications. A similar aspect applies in the case of PEG, where the hydrophilic shell in micelles resulted in longer circulation times within the bloodstream due to reduced recognition by RES and reduced protein adsorption-a phenomenon well known as the "stealth" effect. Because of the stealth property, polymeric micelles avoid recognition by the body's immune system, allowing their favored accumulation in places such as tumors via the enhanced permeability and retention effect (28). Attachment of targeting ligands like antibodies, peptides, or small molecules on the surface of polymeric micelles can allow them to target cell types or tissues. The fact that micelles target certain receptors expressed on the cellular membrane leads to receptor-mediated endocytosis, which enhances the delivery of encapsulated drugs at the active site.

Like most of the other nanoparticles, polymeric micelles can also adsorb proteins from the biological fluids onto their surface; this process is named the so-called protein corona. It is actually this protein layer that can dramatically alter the biological identity of micelles and hence their biodistribution, cellular uptake, and overall therapeutic efficacy (21). It also depends a lot on physical-chemical properties of the micelles, such as their size, surface charge, hydrophilicity of the surface. Presence of PEG on the micelle surface was reported to prevent protein adsorption, and thus preserves stealth character of micelles and extends circulation time. In another situation, protein corona may alter the active targeting capability of functionalized micelles. Adsorbed proteins reduce specific interactions mediated by targeting ligands on the surface of micelles (29). Therefore, the development and regulation regarding a protein corona should be taken into account for optimizing design and performance in the biomedical application of polymeric micelles.

Indeed, the polymeric micelles are highly versatile and powerful platforms in drug delivery, especially for hydrophobic drugs that could not be formulated by other conventional methods. This unique core-shell structure, together with the possibility of surface modification for targeted delivery and long circulation, makes it an attractive choice for manifold therapeutic applications.

4. Dendrimers Some recent innovations in herbal oil extraction

Dendrimers are a unique class of synthetic polymers with highly branched structures in a tree-like configuration. They are formed by the central core from which layers, otherwise known as generations, emanate as symmetric, three-dimensional architecture. Well-defined and controlled architecture, unlike in other classes of polymers pays a high dividend in their versatility for a range of biomedical applications in drug delivery, gene therapy, and diagnostic imaging.

The general structure of dendrimers can be based on a wide variety of monomers; among the most investigated, there are poly(amidoamine) and poly(propylene imine) dendrimers. The surface functional groups of dendrimers can be modified with a wide range of chemical moieties comprising drugs, targeting ligands, or imaging agents, with aims at enhancing the interaction with biological systems (30). Hydrophobic drugs included within the internal cavities of dendrimers exhibit increased solubility and stability. This property is particularly helpful in drugs with low water solubility, wherein the bioavailability is enhanced by dendrimers to make them more therapeutically effective. More interestingly, dendrimers could be prepared to release drugs in response to changes in pH, temperature, or enzymatic activity, enabling targeting of drugs with reduced systemic toxicity (31).

4.1. Interaction with Biological Macromolecules

Interactions of dendrimers with proteins, nucleic acids, and lipids among other biological macromolecules preordinate their fate within the biological system. In general, the nature of the interactions is controlled by the size of the dendrimer, its overall charge, and the nature of its surface functionality (32).

The interactions between dendrimers and proteins are through electrostatic, hydrogen bonding, or hydrophobic interactions, resulting in the formation of complexes. The latter can cause changes in the protein conformation, activity, or stability. For example, negatively charged proteins interact with positively charged dendrimers, which may result in protein aggregation or denaturation. However, chemical modifications on the surface of dendrimers reduce such interaction, for example, PEGylation enhances its biocompatibility (33).

Nucleic Acid Interactions: Dendrimers are especially handy for gene delivery because of the possibility of the interaction between dendrimers with nucleic acids-DNA and RNA-by complexation. Most of the dendrimers have a positive charge on their surface, which participates in electrostatic interactions with the negatively charged phosphate backbone of nucleic acids, by which stable dendrimer-nucleic acid complexes, so-called polyplexes, are formed (34). These complexes can protect the nucleic acids from enzymatic degradation and promote their cellular uptake, hence making dendrimers prospective vectors in gene therapy. one of the important factors concerning their cellular uptake and delivery efficiency is interactions of dendrimers with cell membrane lipid bilayers (20). The nature of the latter depends on the surface charge and hydrophobicity of the dendrimer. Water-soluble cationic dendrimers are, in fact, able to interact and disrupt the packing of lipid bilayers, facilitating membrane destabilization and cellular penetration. This particular property has now led to cytotoxicity. These effects have been overcome through the design of neutral or anionic surface modifications that minimize membrane disruption and support effective cellular delivery (35).

4.2. Dendrimer-Based Therapeutics and Diagnostics

Dendrimers have exhibited huge potentials in a wide range of therapeutic and diagnostic modalities. Targeting drug delivery with dendrimers into particular tissues is achieved either through the modification of a number of targeting ligands on their surface, such as antibodies, peptides, and small molecules. Such targeted deliveries will have immense specificity at the site of action and lessen off-target aspects, hence increasing the therapeutic benefit of the therapeutic agent. This minimizes off-target effects and enhances the therapeutic benefit of the therapeutic agent by targeting drugs to appropriate tissues (36). Applications include gene therapy, where nucleic acids are being delivered into target cells using dendrimers as non-viral vectors. Their

workability regarding protection against the degradation of nucleic acids and efficient cellular entry makes them a superior option compared to viral vectors because of the safety concerns about immunogenicity and insertional mutagenesis. Other uses of dendrimers could be in diagnostic imaging, where they may be coupled with contrast media or fluorescent dyes for MRI techniques (37). Multivalency allows multiple imaging agents to combine onto a dendrimer and, hence amplifies the intensity of the signal toward sensitive detection of a disease state. Materials like MNPs would therefore be of huge interest in diagnosis.

5. Metal-based Nanoparticles (MNP)

Metal-based nanoparticles can refer to a broad, extremely important category of nanomaterials that have cores from metallic elements among which one can find the most included categories such as gold, silver, iron, platinum, and zinc oxide. These nanoparticles have special other physicochemical reactivity, including SPR, large surface area-to-volume ratio, and interaction in a size- and sometimes shape-dependent way with biological molecules. Properties like these make MNPs particularly useful in a wide range of applications that include drug delivery, imaging, and diagnostics, besides their use as therapeutic agents themselves in areas such as oncology and antimicrobial therapy.

5.1. Interaction with Biological Systems

Metallic nanoparticles interact with biological systems through their size, shape, surface charge, and coating. Each of these factors plays a very important role in determining their biocompatibility, biodistribution, cellular uptake, and ultimately their overall therapeutic efficacy (38).

Cellular Uptake: Size, shape, and surface properties are the major determinants for proper cellular uptake of MNPs. The smaller nanoparticles possess a size of less than 100 nm, and hence easily pass through the cellular membranes with mechanisms of endocytosis. Larger particles require special mechanisms of uptake or may remain at the surface of cells. More precisely, modifications to the surface, like ligand attachment-that is, targeting to specific cells or tissues-increase the therapeutic index; for example, antibodies or peptides (39).

The interaction with biomolecules after MNPs enters the biological environment involves the immediate adsorption of various proteins and other biomolecules to form protein corona. This might alter the surface properties of the nanoparticles and determine their interaction with cells, biodistribution, and immune recognition. The composition of the protein corona is rather dynamic and strongly depends on the size, shape, and surface chemistry of MNPs (40).

The most relevant problems related to MNPs concern biocompatibility and cytotoxicity, with particular reference to the case of systemic administration. Thanks to the intrinsic properties of the metal core, cytotoxic effects can be induced-for example, through the release of toxic metal ions by AgNPs, Ag^{+}- or through the generation of reactive oxygen species able to induce oxidative stress and cell damage. While such effects can be considerably reduced through surface modification, either by PEGylation to reduce the binding sites for serum proteins, or by coating with polymers that have biocompatible properties to reduce the MNPs' direct contact with cellular components.

Imaging: MNPs go through a wide range of applications in diagnostic imaging due to their unique optical and magnetic properties. AuNPs have very strong surface plasmon resonance and therefore are suitable for application in optical imaging techniques such as SERS-surface-enhanced Raman scattering, photoacoustic imaging. IONPs are used as MRI contrasting agents whose magnetic properties improve the contrasts between different tissues and hence enhance the resolution of

images taken.

Therapeutic agent: Besides drug carriers, MNPs can act as a therapeutic agent per se. For instance, AgNPs have been used in wound dressings and coating of medical devices due to its broad-spectrum antimicrobial activity. AuNP has also been studied in photothermal therapy where NPs absorb light and convert it into heat so as to selectively destroy cancer cells. Also, some MNPs were designed for their catalytic properties and applied in some cancer treatments in conjunction with other diseases (41).

Theranostics: This is a rapidly growing area of research pertaining to the combination of a diagnostic with a therapeutic function on one single nanoparticle platform known as the theranostics. Due to the possibility of combining the imaging and therapeutic functions under single navigation, MNPs are uniquely suitable for such purposes of theranostics. In this sense, AuNPs would serve in SERS imaging and photothermal treatment, thus enabling in real time the monitoring of the response of the treatment. With regards to this, IONPs may be used for MRI imaging and for targeted drug delivery, thus providing a more multifunctional approach in disease management.

Among all the nanoparticles, the metal nanoparticles probably represent one of the most useful and versatile tools in nanomedicine. The unique advantages of metal nanoparticles have a wide range of applications in drug delivery, imaging, and therapeutic applications. Due to their controlled and targeted interaction with biological systems, they have great value in the development of next-generation diagnostics and therapeutics.

6. Carbon Nanotubes (CNTs)

Carbon nanotubes represent one of the most interesting and versatile classes of nanomaterials. This is due to their exceptional mechanical, electrical, and thermal properties. Structurally, CNTs are cylindrical molecules composed of rolled-up sheets of single-layer carbon atoms or graphene. Those also may be separated into two general categories depending on the number of layers of graphene: SWCNT and MWCNT. The properties variable for CNTs render them highly suitable in very wide ranges of applications-from the material sciences and electronics to biotechnology and medicine.

6.1. Structural Characteristics and Properties

The single-walled carbon nanotubes consist of a graphene sheet rolled onto a cylindrical tube with a diameter normally from 0.8 to 2 nm. Depending on chiralities, the angle at which the graphene sheet has been rolled, they hold exceptional electronic properties and, hence, an ability to conduct like metals or semiconductors. This makes SWCNTs of great importance in such areas as nanoelectronics and as components in field-effect transistors, FETs (42).

Multi-Walled Carbon Nanotubes: MWCNTs basically consist of a number of concentric graphene cylinders nested inside one another, with their diameters lying in the range of 2 to 100 nm. In MWCNTs, the spacing between successive layers has the same value as that between graphene layers in graphite, approximately 0.34 nm. Normally, MWCNTs are stronger and easier to synthesize than SWCNTs, which makes this material more feasible for industrial-scale applications. However, its electronic properties are less well defined compared with the electronic properties of SWCNTs (43).

6.2. Interactions with Biological Systems Cellular Internalization

The interactions of CNT with biological systems depend on several factors, such as size, shape, surface charge, and functionalization of the CNT. According to cell type and surface properties, the functionalized CNTs penetrate into the cells either by the pathway of endocytosis or directly across cell membranes. Their intracellular fate depends, as it will be

discussed later, on surface modification and targeting strategies, determining whether they localize in the cytoplasm or in the nucleus.

6.3. Toxicity and Biocompatibility

Although CNTs have enormous potential for medicine and biomedicine, it is their toxicity which might handicap the great application possibilities. Pristine CNTs are hydrophobic, while, due to fiber morphology, may cause oxidative stress, inflammation, and cytotoxicity, with the aspect ratio similar to asbestos fibers. Nevertheless, the aspect can be reduced by surface functionalization and thus improve biocompatibility in drug delivery, imaging, and tissue engineering applications.

Drug Delivery: Targeting the high surface area, capability for cell internalization, and possibilities for functionalization of CNTs served as a requirement for study in the application of CNTs as drug delivery vectors. Drugs can be loaded onto the CNT surface either through covalent attachment or through noncovalent interactions, such as π-π stacking (44). Functionalized CNTs can be rendered capable of targeting cells or tissues with particular features, thus allowing therapeutic agents to be delivered in a very precise way. Such an approach appears very appealing in cancer treatment, whereby CNTs are allowed to deliver the chemotherapeutic drugs inside the tumor cells while minimizing systemic toxicity. Biosensors and Imaging: The unique electronic and optical properties of CNTs are amenable to biosensors and other imaging applications. The sensors prepared from CNTs, owing to their transducing capability of biological events into quantifiable electrical signals, exhibit ultrasensitivity and high specificity in the detection of biomolecules. Besides, due to the strong absorption capability of CNTs in the NIR region, CNTs can act as contrasting agents in a few modes of imaging, for instance, in NIR fluorescence imaging, thereby enhancing good imaging of biological tissues (45).

Carbon nanotubes represent one of the most promising classes of nanomaterials whose unique properties find applications in almost all sections of materials science, electronics, and biotechnology. Within the biomedical sector, some key CNTs apply in the fields of drug delivery, tissue engineering, and cancer therapy. However, toxic and scalability issues have hampered the improvements in the use of CNTs for therapy. It is the necessary research and innovations to overcome these obstacles that will ensure this promising nanomaterial becomes functional in medicine and beyond.

7. Safety and Toxicology Considerations

While NPs offer significant biomedical advantages, their potential toxicity and long-term effects must be carefully evaluated. Studies on biodistribution, accumulation, and elimination are essential to ensure the safety of NP-based therapies (46). Comprehensive toxicity studies assess the impact of NPs on different organs and systems, identifying potential risks. Regulatory agencies have developed guidelines for evaluating and approving NP-based products to ensure their safety and efficacy.

8. Conclusion

Nanoparticles interact with biological systems at multiple levels, from molecular to tissue interactions. These interactions are complex and influenced by the physicochemical properties of the NPs. Understanding these mechanisms is crucial for developing safe and effective nanomedicines. Future research should focus on elucidating these interactions in greater detail and developing strategies to mitigate potential risks associated with NP exposure.

Acknowledgements

Authors are thankful to the management of RL Jalappa College of Pharmacy (SDUAHER),

Tamaka, Kolar for providing facilities to prepare this manuscript.

Authors Contributions

AKBS: Concept; MK: writing the manuscript; DNS: designing and editing the manuscript; CA:designing and editing the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Pati R, Shevtsov M, Sonawane A. Nanoparticle Vaccines Against Infectious Diseases. *Front Immunol.* 2018 Oct 4;9:2224. doi: 10.3389/fimmu.2018.02224. PMID: 30337923; PMCID: PMC6180194.

2. Casals E, Pfaller T, Duschl A, Oostingh GJ, Puntes V. Time evolution of the nanoparticle protein corona. *ACS Nano*. 2010 Jul 27;4(7):3623-32. doi: 10.1021/nn901372t. PMID: 20553005.

3. Mu Q, Jiang G, Chen L, Zhou H, Fourches D, Tropsha A, Yan B. Chemical basis of interactions between engineered nanoparticles and biological systems. *Chem Rev*. 2014 Aug 13;114(15):7740-81. doi: 10.1021/cr400295a. Epub 2014 Jun 13. PMID: 24927254; PMCID: PMC4578874.

4. Monopoli MP, Aberg C, Salvati A, Dawson KA. Biomolecular coronas provide the biological identity of nanosized materials. *Nat Nanotechnol.* 2012 Dec;7(12):779-86. doi: 10.1038/nnano.2012.207. PMID: 23212421.

5. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. *Adv Drug Deliv Rev*. 2013 Jan;65(1):36-48. doi: 10.1016/j.addr.2012.09.037. Epub 2012 Oct 1. PMID: 23036225.

6. Choi HS, Liu W, Misra P, Tanaka E, Zimmer JP, Itty Ipe B, Bawendi MG, Frangioni JV. Renal clearance of quantum dots. *Nat Biotechnol*. 2007 Oct;25(10):1165-70. doi: 10.1038/nbt1340. Epub 2007 Sep 23. PMID: 17891134; PMCID: PMC2702539.

7. Kanasty R, Dorkin JR, Vegas A, Anderson D. Delivery materials for siRNA therapeutics. *Nat Mater.* 2013 Nov;12(11):967-77. doi: 10.1038/nmat3765. PMID: 24150415.

8. Kranz LM, Diken M, Haas H, Kreiter S, Loquai C, Reuter KC, et al. Systemic RNA delivery to dendritic cells exploits antiviral defence for cancer immunotherapy. *Nature*. 2016 Jun 16;534(7607):396-401. doi: 10.1038/nature18300. Epub 2016 Jun 1. PMID: 27281205.

9. Zhao X, Ng S, Heng BC, Guo J, Ma L, Tan TT, Ng KW, Loo SC. Cytotoxicity of hydroxyapatite nanoparticles is shape and cell dependent. *Arch Toxicol.* 2013 Jun;87(6):1037-52. doi: 10.1007/s00204-012-0827-1. Epub 2012 Mar 14. PMID: 22415765.

10. Oh N, Park JH. Endocytosis and exocytosis of nanoparticles in mammalian cells. *Int J Nanomedicine.* 2014 May 6;9 Suppl 1(Suppl 1):51-63. doi: 10.2147/IJN.S26592. PMID: 24872703; PMCID: PMC4024976.

11. Kim JA, Åberg C, Salvati A, Dawson KA. Role of cell cycle on the cellular uptake and dilution of nanoparticles in a cell population. *Nat Nanotechnol.* 2011 Nov 6;7(1):62-8. doi: 10.1038/nnano.2011.191. PMID: 22056728.

12. Derfus AM, Chan WCW, Bhatia SN. Probing the Cytotoxicity Of Semiconductor Quantum Dots. *Nano Lett.* 2004 Jan 1;4(1):11-18. doi: 10.1021/nl0347334. Epub 2003 Dec 10. PMID: 28890669; PMCID: PMC5588688.

13. Gao W, Wang Y, Xiong Y, Sun L, Wang L, Wang K, et al. Size-dependent anti-inflammatory activity of a peptide-gold nanoparticle hybrid in vitro and in a mouse model of acute lung injury. *Acta Biomater.* 2019 Feb;85:203-217. doi: 10.1016/j.actbio.2018.12.046. Epub 2018 Dec 28. PMID: 30597258; PMCID: PMC8960115.

14. Gabizon A, Shmeeda H, Barenholz Y. Pharmacokinetics of pegylated liposomal Doxorubicin: review of animal and human studies. *Clin Pharmacokinet*. 2003;42(5):419-36. doi: 10.2165/00003088-200342050-00002. PMID: 12739982.

15. Moghimi SM, Hunter AC, Murray JC. Long-circulating and target-specific nanoparticles: theory to practice. *Pharmacol Rev.* 2001 Jun;53(2):283-318. PMID: 11356986.

16. Kreuter J. Nanoparticulate systems for brain delivery of drugs. *Adv Drug Deliv Rev.* 2001 Mar 23;47(1):65-81. doi: 10.1016/s0169-409x(00)00122-8. PMID: 11251246.

17. Dobrovolskaia MA, McNeil SE. Immunological properties of engineered nanomateri-

als. *Nat Nanotechnol.* 2007 Aug;2(8):469-78. doi: 10.1038/nnano.2007.223. Epub 2007 Jul 29. PMID: 18654343.
18. Alric C, Miladi I, Kryza D, Taleb J, Lux F, Bazzi R, et al. The biodistribution of gold nanoparticles designed for renal clearance. *Nanoscale*. 2013;5(13):5930-9.
19. Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. *Adv Drug Deliv Rev*. 2002 Sep 13;54(5):631-51. doi: 10.1016/s0169-409x(02)00044-3. PMID: 12204596.
20. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nat Biotechnol.* 2015 Sep;33(9):941-51. doi: 10.1038/nbt.3330. PMID: 26348965; PMCID: PMC4978509.
21. Danhier F, Ansorena E, Silva JM, Coco R, Le Breton A, Préat V. PLGA-based nanoparticles: an overview of biomedical applications. *J Control Release*. 2012 Jul 20;161(2):505-22. doi: 10.1016/j.jconrel.2012.01.043. Epub 2012 Feb 4. PMID: 22353619.
22. Gillies ER, Fréchet JM. Dendrimers and dendritic polymers in drug delivery. *Drug Discov Today.* 2005 Jan 1;10(1):35-43. doi: 10.1016/S1359-6446(04)03276-3. PMID: 15676297.
23. Gref R, Minamitake Y, Peracchia MT, Trubetskoy V, Torchilin V, Langer R. Biodegradable long-circulating polymeric nanospheres. *Science.* 1994 Mar 18;263(5153):1600-3. doi: 10.1126/science.8128245. PMID: 8128245.
24. Lundqvist M, Stigler J, Elia G, Lynch I, Cedervall T, Dawson KA. Nanoparticle size and surface properties determine the protein corona with possible implications for biological impacts. *Proc Natl Acad Sci U S A*. 2008 Sep 23;105(38):14265-70. doi: 10.1073/pnas.0805135105. Epub 2008 Sep 22. PMID: 18809927; PMCID: PMC2567179.
25. Allen TM, Cullis PR. Drug delivery systems: entering the mainstream. *Science.* 2004 Mar 19;303(5665):1818-22. doi: 10.1126/science.1095833. PMID: 15031496.
26. Cedervall T, Lynch I, Lindman S, Berggård T, Thulin E, Nilsson H, et al. Understanding the nanoparticle-protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles. *Proc Natl Acad Sci U S A*. 2007 Feb 13;104(7):2050-5. doi: 10.1073/pnas.0608582104. Epub 2007 Jan 31. PMID: 17267609; PMCID: PMC1892985.
27. Kataoka K, Harada A, Nagasaki Y. Block copolymer micelles for drug delivery: design, characterization and biological significance. *Adv Drug Deliv Rev*. 2001 Mar 23;47(1):113-31. doi: 10.1016/s0169-409x(00)00124-1. PMID: 11251249.
28. Kwon GS, Kataoka K. Block copolymer micelles as long-circulating drug vehicles. *Adv Drug Deliv Rev*. 1995;16(2-3):295-309.
29. Matsumura Y, Kataoka K. Preclinical and clinical studies of anticancer agent-incorporating polymer micelles. *Cancer Sci.* 2009 Apr;100(4):572-9. doi: 10.1111/j.1349-7006.2009.01103.x. PMID: 19462526; PMCID: PMC11158079.
30. Oerlemans C, Bult W, Bos M, Storm G, Nijsen JF, Hennink WE. Polymeric micelles in anticancer therapy: targeting, imaging and triggered release. *Pharm Res*. 2010 Dec;27(12):2569-89. doi: 10.1007/s11095-010-0233-4. Epub 2010 Aug 20. PMID: 20725771; PMCID: PMC2982955.
31. Salvati A, Pitek AS, Monopoli MP, Prapainop K, Bombelli FB, Hristov DR, et al. Transferrin-functionalized nanoparticles lose their targeting capabilities when a biomolecule corona adsorbs on the surface. *Nat Nanotechnol.* 2013 Feb;8(2):137-43. doi: 10.1038/nnano.2012.237. Epub 2013 Jan 20. PMID: 23334168.
32. Torchilin VP. Micellar nanocarriers: pharmaceutical perspectives. *Pharm Res*. 2007 Jan;24(1):1-16. doi: 10.1007/s11095-006-9132-0. Epub 2006 Nov 16. PMID: 17109211.
33. Fréchet JM. Functional polymers and dendrimers: reactivity, molecular architecture, and interfacial energy. *Science.* 1994 Mar 25;263(5154):1710-5. doi: 10.1126/science.8134834. PMID: 8134834.
34. Kobayashi H, Brechbiel MW. Dendrimer-based nanosized MRI contrast agents. *Curr Pharm Biotechnol*. 2004 Dec;5(6):539-49. doi: 10.2174/1389201043376571. PMID: 15579043.
35. Kukowska-Latallo JF, Candido KA, Cao Z, Nigavekar SS, Majoros IJ, Thomas TP, et al. Nanoparticle targeting of anticancer drug improves therapeutic response in animal model of human epithelial cancer. *Cancer Res.* 2005 Jun 15;65(12):5317-24. doi: 10.1158/0008-5472.CAN-04-3921. PMID: 15958579.
36. Lee CC, MacKay JA, Fréchet JM, Szoka

FC. Designing dendrimers for biological applications. *Nat Biotechnol.* 2005 Dec;23(12):1517-26. doi: 10.1038/nbt1171. PMID: 16333296.

37. Malik N, Evagorou EG, Duncan R. Dendrimer-platinate: a novel approach to cancer chemotherapy. *Anticancer Drugs*. 1999 Sep;10(8):767-76. PMID: 10573209.

38. Majoros IJ, Thomas TP, Mehta CB, Baker JR Jr. Poly(amidoamine) dendrimer-based multifunctional engineered nanodevice for cancer therapy. *J Med Chem*. 2005 Sep 22;48(19):5892-9. doi: 10.1021/jm0401863. PMID: 16161993.

39. Mecke A, Uppuluri S, Sassanella TM, Lee DK, Ramamoorthy A, Baker JR Jr, Orr BG, Banaszak Holl MM. Direct observation of lipid bilayer disruption by poly(amidoamine) dendrimers. *Chem Phys Lipids.* 2004 Nov;132(1):3-14. doi: 10.1016/j.chemphyslip.2004.09.001. PMID: 15530443.

40. Patri AK, Majoros IJ, Baker JR. Dendritic polymer macromolecular carriers for drug delivery. *Curr Opin Chem Biol*. 2002 Aug;6(4):466-71. doi: 10.1016/s1367-5931(02)00347-2. PMID: 12133722.

41. Tomalia DA, Reyna LA, Svenson S. Dendrimers as multi-purpose nanodevices for oncology drug delivery and diagnostic imaging. *Biochem Soc Trans*. 2007 Feb;35(Pt 1):61-7. doi: 10.1042/BST0350061. PMID: 17233602.

42. Chithrani BD, Ghazani AA, Chan WC. Determining the size and shape dependence of gold nanoparticle uptake into mammalian cells. *Nano Lett.* 2006 Apr;6(4):662-8. doi: 10.1021/nl052396o. PMID: 16608261.

43. Dykman LA, Khlebtsov NG. Gold nanoparticles in biology and medicine: recent advances and prospects. *Acta Naturae.* 2011 Apr;3(2):34-55. PMID: 22649683; PMCID: PMC3347577.

44. Avouris P, Chen Z, Perebeinos V. Carbon-based electronics. *Nat Nanotechnol*. 2007 Oct;2(10):605-15. doi: 10.1038/nnano.2007.300. Epub 2007 Sep 30. PMID: 18654384.

45. Berber S, Kwon Y-K, Tománek D. Unusually High Thermal Conductivity of Carbon Nanotubes. *Phys Rev Lett*. 2000;84(20):4613-6.

46. Cassell AM, Raymakers JA, Kong J, Dai H. Large scale CVD synthesis of single-walled carbon nanotubes. *J Phys Chem B*. 1999;103(31):6484-92.